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A Critical Evaluation of U.S. EPA's

Hazard Ranking System

Score Calculated for Lead

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1 Introduction

This report critically evaluates the toxicity factor value calculated for lead by EPA for use in the Agency's Hazard Ranking System (HRS). In brief, we demonstrate that EPA has developed an HRS toxicity factor value for lead that substantially overstates the risk of lead relative to the risk posed by other chemicals. This report proposes an alternative calculation of the toxicity factor value for lead. Our alternative methodology is consistent with other EPA guidance for lead, including Soil Screening Levels (SSL), National Ambient Air Quality Standards (NAAQS), and Maximum Contamination Levels (MCL) for drinking water.

The remainder of this report. has five sections. Section 2 provides an overview of the methodology used to develop toxicity factor values in the context of the Agency's 1990 final rule describing the HRS, and in the context of HRS as modified for use with EPA's Sector Facility Indexing Project (SFIP). Section 3 compares lead's toxicity to the toxicity of other chemicals regulated by EPA, demonstrating that the toxicity factor value assigned to lead is too high relative to the scores assigned other chemicals. Section 4 describes EPA's use of the Integrated Exposure Uptake Biokinetic (IEUBK) Model to evaluate lead toxicity in numerous settings. Based on this information, Section 5 derives an alternative toxicity factor value for lead. Finally, Section 6 demonstrates that our calculation of an alternative toxicity factor value for lead is consistent with toxicological knowledge and hence improves the scientific basis of the risk scores calculated as part of EPA's HRS and SFIP.

2 The Development of Toxicity Factor Values, Hazard Ranking Scores, and Their Use in Ranking Facilities

This section describes the Hazard Ranking System (HRS) that EPA has adopted (Section 2.1), and Agency modifications to the HRS specific to its use in the context of the SFIP (Section 2.2).

2.1 EPA's Hazard Ranking System

EPA's Hazard Ranking System (HRS) was developed to assign scores to hazardous waste sites so that they could be ranked in terms of the health hazard they posed to human populations. Those scores have been used to determine which such sites are included on the National Priority List (NPL). A site's placement on the NPL is likely to result in considerable costs being incurred for human health and environmental investigative studies and associated activities to remedy the contamination identified by those studies. EPA's HRS also serves as the basis for the derivation of toxicity weighting factors used in the context of EPA's SFIP.

The HRS was first adopted in 1982 by EPA as part of the Agency's program to develop the NPL. In a Federal Register notice, EPA described the most recent revision to the HRS (U.S. EPA, 1990a). The notice describes the calculation of human toxicity factors (referred to hereafter as "toxicity factors") for both non-carcinogens and for carcinogens. Tables 2-la and b (below) reproduce the scheme described by EPA.

Table 2-la
The EPA'S Hazard Ranking System: Non-Carcinogens

Reference Dose (RfD) (mgkg-day)	Toxicity Factor Value Assigned
IUD < 0.0005	10,000
0.0005 ≤ IUD < 0.005	1,000
0.005 ≤ IUD < 0.05	100
0.05 ≤ IUD < 0.5	10
0.5 ≤ IUD	1
IUD not available	0

Adapted from Table 2-4 in U.S. EPA (1990a).

Table 2-lb
The **EPA's Hazard** Ranking **System:** Carcinogens

Weight-of-evidence and slope factor (SF) in (mg/kg-day)$^{-1}$			
A	B	C	Assigned Value
0.5 ≤ SF	5 ≤ SF	50 ≤ SF	10,000
0.05 ≤ SF < 0.5	0.5 ≤ SF < 5	5 ≤ SF < 50	1,000
SF < 0.05	0.05 ≤ SF < 0.5	0.5 ≤ SF < 5	100
-	SF < 0.05	SF < 0.5	10
	Slope factor not available		*0*

Adapted from Table 2-4 in U.S. EPA (1990a).

The Agency specifies several additional rules for the assignment of toxicity factor values:

- **For** chemicals exhibiting both carcinogenic and non-carcinogenic health effects, **the** toxicity factor is assigned a value equal to the maximum score calculated for either health endpoint.
- If all chemicals for a specific exposure pathway have a toxicity factor value of 0, then the HRS protocol dictates that the pathway be assigned a toxicity factor value of 100.
- **For** substances having usable toxicity data for multiple exposure routes, the toxicity factor is assigned a value equal to the maximum score calculated for any route.
- "If neither an RfD nor slope factor nor accurate toxicity value is available, assign the hazardous substance **an** overall toxicity factor value of **zero** and **use** other hazardous substances for which information is available in evaluating the pathway" **(40 CFR** Part **300,** Appendix **A,** Paragraph **2.4.1.1).**
- Lead and **asbestos** are assigned a toxicity factor value of 10,000.

Of particular interest in this report is the Agency's treatment of lead. A 1990 memo by Dr. Larry J. Zaragoza, (U.S. EPA, 1990b) provides the EPA's rationale for its assignment to lead of the maximum possible toxicity factor value of 10,000. **The** memo outlines **three** reasons for EPA's special treatment of lead. Specifically, EPA (1990b, p. **2)** states that, "*Lead is assigned the maximum toxicity value of 10,000 for scoring purposes in the revised HRS for the following reasons:*

- *the absence of a demonstrated threshold for systemic toxicity*
- *the cumulative sequestration of lead in the bone matrix and its subsequent release during pregnancy or osteoporosis*
- *the absence of an RfD and a cancer factor would give lead a toxicity factor value of 0 under the revised HRS which is inconsistent with the known health effects.-*

2.2 Modifications to EPA's Hazard Ranking System for the SFIP

A 1997 memo by Steven A. Herman (U.S. EPA, 1997) details the assignment of toxicity factor values in the context of the SFIP in Attachment 2 of his memo. The SFIP HRS differs from the original HRS as follows:

- The SFIP extends the range of cancer slope factors and RfD values explicitly addressed, creating additional toxicity factor value "bins." These new categories can have toxicity factor values substantially exceeding the original HRS maximum value of 10,000 (see Tables 2-la and 2-1b, above). Hence, the SFIP puts much greater emphasis on chemicals with especially high cancer slope factors or especially low RfD values.
- The SFIP treats weight-of-evidence category A and B carcinogens identically. Specifically, both are assigned the same score as is assigned by the original HRS to category A carcinogens. A factor of 10 separates the toxicity factor value scores assigned to category A and category C carcinogens in the SFIP HRS, in contrast to the factor of 100 separating such values in the original HRS scheme.

Tables 2-2a and 2-2b below detail the SFIP toxicity factor assignment scheme.

Table 2-2a
The EPA's SFIP Hazard Ranking System: Non-Carcinogens

Reference Dose (RfD) (mg/kg-day)	Toxicity Factor Value Assigned
RfD < *0.00005*	100,000
0.00005 ≤ RfD < *0.0005*	10,000
0.0005 5 RfD < 0.005	1,000
0.005 ≤ RfD < *0.05*	100
0.05 5 RfD < 0.5	10
0.5 ≤ RfD	

Adapted from Exhibit 6 in U.S. EPA (1997), Attachment 2.

Table 2-2b
The EPA's SFIP Hazard Ranking System: Carcinogens

Slope factor (mg/kg-day)$^{-1}$	Weight of Evidence Category	
	A/B (known/probable)	C (possible)
< 0.005	10	1
0.005 to 0.05	100	10
0.05 to *0.5*	1,000	100
0.5 to *5*	10.000	1000
5 to 50	100,000	10,000
> *50*	1,000,000	100,000

Several points related to these tables must be noted. First, the first row of Table 2-2a (which assigns a toxicity factor value of 100,000 to chemicals with an RfD below 0.00005 mg/kg-day) has been added to Table 2-1a (above), which describes the assignment of toxicity factor values in the original HRS. Second, the last row of Table 2-1a (above), which assigns a toxicity factor value of zero to chemicals for which there is insufficient information *to* determine an RfD, has been eliminated from Table 2-2a. Third, footnote 1 on page 12 of Attachment 2 (U.S. EPA, 1997) states that the SFIP HRS does not assign a default toxicity factor value of 10,000 to lead and asbestos.

Of particular interest in this report is the assignment of a toxicity factor value of 100,000 to lead compounds (see page 8 in Attachment 3 of U.S. EPA, 1997) in contrast to the value of 10,000 assigned to lead in the original HRS.

3 EPA's Characterization of Lead's Toxicity in the Context of Setting Exposure Standards

This section discusses EPA's approach to setting standards for lead exposure in the context of soil (EPA's SSLs), air (EPA's NAAQS values), and water (EPA's MCLs). In these cases, the Agency evaluates standards so as to protect the population from exposures that may result in blood lead levels exceeding a health-based threshold. In a 1991 statement (U.S. CDC, 1991), CDC identified this threshold to be 10 µg/dL. Section 3.1 discusses the Agency's SSL, NAAQS, and MCL criteria for lead. In Section 3.2, we compare the SSL criteria for several chemicals, including lead, to their toxicity factor values. This comparison demonstrates that the toxicity factor value for lead vastly overstates the

potential hazard it poses to human health, when compared to the standards established by these risk-based standards.

3.1 EPA's Establishment of SSLs, NAAQS Values, and MCL Values for Lead

3.1.1 EPA's SSL for Lead

Simply stated, EPA's SSLs "are risk-based concentrations derived from equations combining exposure information assumptions with EPA toxicity data" (U.S. EPA, 1996a, p. 1). In other words, SSLs are maximum soil contamination levels consistent with acceptable human risk estimates that take both exposure and toxicity into account'. Given identical exposure assumptions, differences in SSL values correspond to differences in estimated toxicity. In other words, the inverse of the ratio of the SSL for chemical A to the SSL for chemical B is approximately equal to the ratio of chemical A's toxicity to chemical B's toxicity'.

The specific rationale underlying EPA's SSL of 400 µg/g for lead is outlined in a directive published by EPA's Office of Solid Waste and Emergency Response (OSWER) (U.S. EPA, 1994a). On page 8 of this directive, the Agency states,

> Development of the residential screening level in this interim directive required two important OSWER decisions. 1) OSWER determined that it would seek to achieve a specific level of protectiveness in site cleanups; generally, OSWER will attempt to limit exposure to soil lead levels such that a typical (or hypothetical child or group of similarly exposed children) would have an estimated risk of no more than 5% of exceeding the 10 µg lead/dL blood lead level. This 10 µg/dL blood lead level is based upon analyses conducted by the Centers for Disease Control and EPA that associate blood lead levels of 10 µg/dL and higher with health effects in children; however, this blood lead level is below a level that would trigger medical intervention. 2) In developing the residential screening level, OSWER has decided to apply the EPA's IEUBK model on a site-specific basis... A screening level that is protective for young children is expected to be protective for older population subgroups.

[1] SSLs are purposely designed to be conservative. "SSLs alone do not *trigger* the need for response actions or defme 'unacceptable' levels of contaminants in soil. ... Generally, where contaminant concentrations qual or exceed SSLs, further study or investigation. but not necessarily cleanup, is warranted" (U.S. EPA, 1996a, p. 1).

[2] Note *that* this statement applies to the SSL based on soil ingestion. Differences in SSLs for the inhalation of soilderived vapors and soilderived atmospheric particulates arise from differences between chemicals in toxicity as well as in the fate and transport processes *that* may subsequently affect other media (*e.g.*, groundwater or air).

3.1.2 EPA's NAAQS for Lead

The Office for Air Quality Planning and Standards reviewed EPA's NAAQS of 1.5 $\mu g/m^3$ for lead (U.S. EPA, 1989). In defining a NAAQS level for lead, the Agency relied on estimating blood lead levels associated with various concentrations of atmospheric lead. On page I-2, U.S. EPA (1989) states that "EPA is assessing health risks associated with lead exposure ... for its review of the [NAAQS] for lead ... A critical element in this process will be an exposure analysis whereby blood lead levels are estimated among populations exposed under alternative lead NAAQS in the future."

The EPA document goes on to describe three approaches for the prediction of blwd lead levels associated with alternative NAAQS, one of which is use of the Agency's Integrated Exposure Uptake Biokinetic (IEUBK) Model to predict blood lead levels. Table 4-1 in U.S. EPA (1989) details the calculation of daily lead uptake (*i.e.*, the quantity of lead absorbed into the body's circulatory system) for NAAQS ranging from 0.25 $\mu g/m^3$ to 1.5 $\mu g/m^3$. The calculations reflect the intake of lead *via* inhalation, dietary lead consumption, and ingestion of lead in soil and dust. Citing research by Chamberlain and Heard, EPA (1989, p. IV-11) quantifies the relationship between the change in blwd lead levels and the change in lead uptake as $\Delta PbB / \Delta Uptake = 0.34$ $\mu g/dL$ per μg lead uptake per day. Multiplying the uptake values in Table 4-1 in U.S. EPA (1989) yields total predicted blood lead levels for each of the alternative NAAQS.

3.1.3 EPA's MCL for Lead

The MCL values set by EPA are health-based standards that also reflect technical feasibility. In the case of lead, EPA established an "action level" of 0.015 mg/L. Specifically, in the Agency's 1991 final rule for the national primary drinking water regulations for lead and copper (U.S. EPA, 1990c), EPA mandates that in public water systems serving at least 50,000 people, the lead level may exceed 0.015 mg/L "in no more than 10 percent of tap samples." Failure to achieve this standard "will trigger corrosion control, ... source water monitoring, public education, and lead service line replacement..." (p. 26490).

EPA states that "an action level of 0.015 mg/L is appropriate because it will trigger treatment when appropriate to protect public health" (p. 26491). In this case, EPA defines its sensitive population to be protected as "young children," and establishes its benchmark "to measure progress toward the goal of reducing lead exposure among sensitive populations [to be] the number of children with blood lead (PbB) levels above 10 µg/dL from all sources" (p. 26491). That is, the Agency states that its evaluation of the 0.015 mg/L MCL reflects the effect that standard will have on the number of children exceeding a blood lead level threshold of 10 µg/dL. In this case, the Agency predicts that for children who are not excessively exposed to lead in paint or soil, the 0.015 mg/L MCL will reduce the number of children with blood lead levels above 10 µg/dL from 3.5 percent to 1.6 percent.

3.2 A Comparison of EPA's SSL Values and Toxicity Factor Values for Lead and Several Other Chemicals

U.S. EPA (U.S. EPA, 1996b, Appendix A) lists generic SSL values for 110 substances. "Generic SSLs are derived using default values in ... standardized [exposure] equations" (U.S. EPA, 1996b, p A-1). That is, the generic SSLs[3] are derived using identical exposure assumptions and hence their differences among chemicals reflect only differences in presumed toxicity. Table 3-1 below lists SSL values and the HRS toxicity factor values for lead, cadmium, and PCBs. Note that these values were developed for the oral exposure pathway.

[3] This statement applies to the SSL based on soil ingestion. As noted earlier, differences in SSLs for inhalation of soilderived vapors and soilderived atmospheric particulates arise from differences between chemicals in toxicity as well as in the fate and transport processes that may subsequently affect other media (*e.g.*, groundwater or air).

Table 3-1
SSL Values and SFIP HRS Toxicity Factor Values for Lead, Cadmium, and PCBs

Chemical	SSL		1990 HRS		HRS for the SFIP	
	Value (µg/g)	Ratio of Other Chemical SSL to Lead SSL	Toxicity Score	HRS Ratio: Lead to Other Chemical	Toxicity Score	HRS Ratio: Lead to Other Chemical
column 1	column 2	column 3	column 4	column 5	column 6	column 7
Lead	400[a]	1.0	10,000	1.0	100,000	1.0
Cadmium	39	0.098	1,000	10.0	1,000	100.0
PCBs	1[b]	0.0025	1,000[c]	10.0	100,000	1.0

Notes:

a. *The screening value for lead is bawd on a multipathway analysis of lead's risk using the Agency's Integrated Exposure Uptake Biokinetic (IEUBK) Model. This model is discussed in further detail in Section 4.*

b. *The PCB SSL value reflects protection against cancer.*

c. *The 1990 HRS value listed here reflects the criteria outlined by EPA and described above in Section 2, along with the current weight-of-evidence classification for PCBs (B2) and the current estimated cancer slope factor for these chemicals. which is 2.0 (mg/kg-day)$^{-1}$ for the upper-bound estimate, or 1.0 (mg/kg-day)$^{-1}$ for the central estimate.*

The ratios listed in columns 3, 5, and 7 of Table 3-1 demonstrate that both sets of HRS toxicity factor values are not consistent with the risk-based SSL criteria. If the HRS toxicity factor values were consistent with the SSL values, the ratios in columns 5 and 7 would be approximately equal to the ratios in column 3. However, the SSL values illustrate that the toxicity of lead is approximately 10% of the toxicity of cadmium, and approximately 0.25% the toxicity of PCBs. The 1990 HRS toxicity factor values, on the other hand, suggest that lead's toxicity exceeds the toxicity of both cadmium and PCBs by a factor of 10. From these comparisons, it is clear that the HRS toxicity values overstate the toxicity of lead.

4 EPA's Use of the IEUBK Model to Evaluate Risks Associated with Lead Exposure

In this section, we discuss specifically how the EPA uses the Agency's Integrated Exposure Uptake Biokmetic (IEUBK) Model to estimate total lead exposure *via* multiple exposure pathways, and how the results are interpreted in order to evaluate the acceptability of the exposure. EPA has

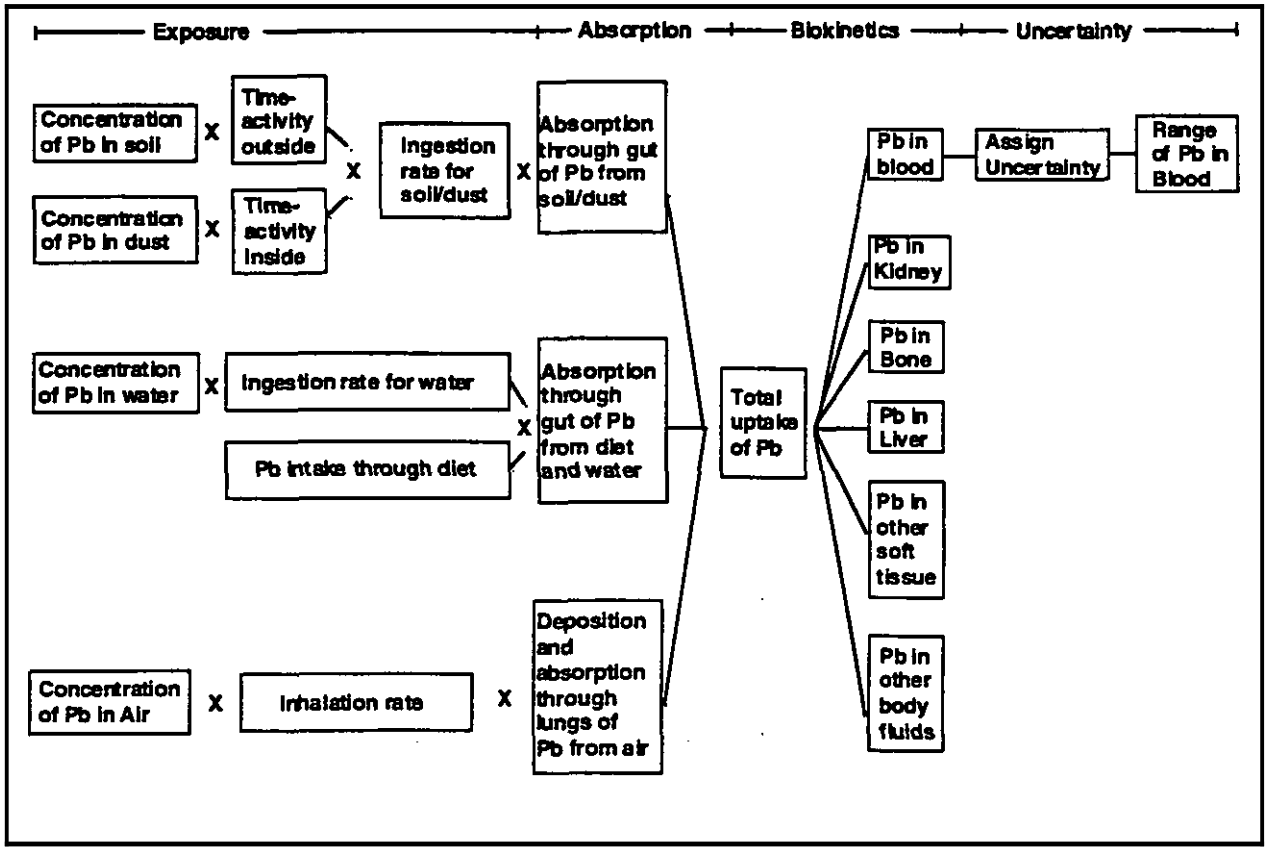
consistently relied on this model to establish standards. Examples include the establishment of SSLs, the establishment of soil cleanup levels pursuant to Section 403 of TSCA (the Toxic Substances Control Act), and the evaluation of Superfund sites and RCRA facilities.

4.1 Overview of the IEUBK Model

The IEUBK Model is a computer-based deterministic simulation that estimates the blood lead concentration in children resulting from their exposure to lead in soil, dust, drinking water, diet, and air. Specifically, the model estimates the intake and uptake of lead into the body and then uses pharmacokinetic modeling to predict blood lead levels.

Figure 4-1 graphically illustrates the model's operation. The exposure component of the model estimates the intake of lead into the body as a function of the concentration of lead in soil, dust, water, and air, the daily ingestion or inhalation rate for these media, and the total amount of lead ingested through diet. The absorption component of the model estimates the fraction of lead taken into the body that is absorbed into the body's circulatory system; for different sources of lead, the value of this fraction may be different. The product of lead intake and the fraction of lead absorbed, summed across exposure media, is equal to total lead uptake. The biokinetic component of the model simulates the transfer of lead among various tissues in the body (including blood, soft tissue, and bone) over time, along with the excretion of lead from the body. Internally, the model keeps track of lead levels in kidney, bone, liver, and so forth. However, the model reports lead levels for only blood. This result is interpreted as the geometric mean blood lead level for a population of hypothetical children subjected to the specified exposure. The variability component of the model uses this geometric mean, along with a specified geometric standard deviation (a measure of spread in the blood lead values) to characterize a complete lognormal distribution of blood lead values.

Figure 4-1
Structure of the US. EPA's Integrated Exposure Uptake Biokinetic (IEUBK) Model for Lead



4.2 EPA's Use of the IEUBK Model

Because lead is present to some degree in all environmental media, and because blood lead levels of individuals will vary even at the same exposure level, at least some individuals will have "elevated" blood lead levels at even "background" levels of lead exposure. Thus, EPA's risk management strategy is to limit exposure so that an individual's risk of having an elevated body lead burden is deemed acceptable. For the soil ingestion pathway, EPA typically limits exposure so that no individual has more than a 5% risk of having a blood lead level exceeding 10 µg/dL. This criterion serves as the basis for EPA's 400 µg/g SSL (see Section 3.1 above). Specifically, U.S. EPA (1994a, p. 10) states that, "EPA recommends that a soil lead concentration be determined so that a typical child or group of children exposed to lead at this level would have an estimated risk of no more than 5% of

exceeding a blood lead of 10 µg/dL." d for maximum t levels of lead in k water and in air have been t in an analogous manner.

In short, U.S. EPA uses the IEUBK Model, together with the 10 µg/dL blood lead threshold, to characterize the toxicity of lead. In the case of the most recent standards discussed in this section (the SSLs), the Agency also specifies that no child's risk of having a blood lead level exceeding 10 µg/dL may be more than 5%'. In Section 5, we use this methodology to calculate a maximum daily intake for lead, and then use this daily intake value to assign an alternative HRS toxicity value.

5 Calculation of an Alternative HRS Lead Toxicity Value

This section first describes use of the EPA's IEUBK Model to calculate a maximum daily intake rate that is consistent with EPA's characterization of lead toxicity, and then identifies the corresponding HRS score (Section 5.1)[5]. Section 5.2 demonstrates that the IEUBK Model used in Section 5.1 is "health protective" in the sense that its predicted blood lead levels exceed empirically measured blood lead levels. Section 5.3 describes why the toxicity factor score calculated in Section 5.1 is appropriate – *i.e.*, why the methodology used to derive that score is consistent with the methodology used to derive HRS scores for other chemicals. Finally, Section 5.4 refutes the rationale advanced by U.S. EPA (1990b) for assigning lead the highest HRS toxicity factor value.

5.1 Calculation of the Alternative HRS Score for Lead

In the following text, we describe our derivation of a maximum acceptable lead intake rate that is consistent with EPA's treatment of lead toxicity. Our calculation reflects information pertaining to lead's non-carcinogenic health effects since EPA assesses risks for lead primarily based on its neurotoxicity in children rather than on its carcinogenicity in animals.

[4] Limiting the individual risk of having a blwd lead level above 10 µg/dL to 5% is a particularly stringent standard since it is more difficult *to* achieve a specified level of risk for each member of a population than it is *to* achieve that level of risk on a population basis. For example, it is more difficult to ensure that no individual has more than a 5% risk of having a blood lead level above 10 µg/dL than it is *to* ensure that no more than 5% of *the* population has a blood lead level exceeding 10 µg/dL.

[5] *Our* calculation uses the EPA's EUBK Model because it is the Agency's standard approach for evaluating lead risks. However, our use of the model here does not constitute an endorsement, since, as detailed in Section 5.2 of this report, the EUBK Model overestimates actual blood lead levels and hence overstates the risks associated with lead exposure.

As described in Section 4, EPA characterizes lead's toxicity in terms of blood lead levels. Blood lead levels below 10 µg/dL are deemed to be acceptable; since human behavior and physiology varies, U.S. EPA has deemed as acceptable a soil exposure low enough to ensure that an individual risk of exceeding 10 µg/dL is no more than 5%.

Appendix A describes use of the IEUBK model to calculate the maximum daily intake of lead consistent with a 5% risk of having a blood lead level exceeding 10 µg/dL. The derivation makes the following assumptions:

- The geometric standard deviation for blood lead levels is 1.7. This assumption is consistent with EPA guidance for the IEUBK Model (U.S. EPA, 1994b);
- The fraction of ingested lead that is absorbed into the body's circulatory system is 40%. This value is midway between the default value for the highly soluble lead found in food and drinking water (50%), and the conservative default assumption for the fraction lead in dust in soil that is absorbed (30%)[6]. Our value of 40% therefore implicitly assumes that approximately half the lead ingested by a child is from food or water, and about half is from soil. Given the substantial drop in dietary lead in the past 10 to 15 years (Bolger. 1996), this assumption is probably conservative.
- The individual evaluated is a child between the ages of 2 and 3 years of age. Children between the ages of 2 and 3 tend to be most susceptible to lead exposure due to behavioral characteristics (hand-to-mouth behavior) and physiological characteristics (young children tend to absorb a greater fraction of ingested lead than older individuals).

The maximum calculated lead intake rate consistent with U.S. EPA's criteria is 28 µg/day. The average weight for a 2-3 year old child is approximately 14 kg. Hence, the maximum acceptable lead intake rate is 28 µg/day ÷ 14 kg, or approximately 2 µg/kg-day (2×10^{-3} mg/kg-day). Table 2-2a in this report details the relationship between RfD values and HRS scores. An HRS score of 1,000 corresponds to an RfD equal to the maximum acceptable intake rate just calculated. This result is a full factor of 10 below the 1990 HRS toxicity factor value for lead, and a factor of 100 below the HRS toxicity factor value for lead developed for EPA's SFTP.

[6] The fraction of lead absorbed from soil and dust can be substantially less than 30%, especially in areas where the soil is derived from mine tailings (See, for example, Steele *et al.*, 1990).

We also note that unless the assumptions we used are substantially (and implausibly) altered, the calculated HRS toxicity factor value for lead remains equal to 1,000. Specifically, note that a chemical with an RfD as low as 5×10^{-4} mg/kg-day is assigned an HRS score of 1,000. Our calculated maximum acceptable daily intake value for lead of 2×10^{-3} exceeds this bound by a factor of 4. Hence, if we had, for example, assumed that 50% of ingested lead is absorbed (which is the maximum fraction EPA assumes is absorbable for any source of lead (U.S. EPA, 1994b)), rather than 40%, we would have calculated a maximum acceptable intake rate of approximately $2 \times 10^{-3} \times (40\% \div 50\%)$, or 1.6×10^{-3} mg/kg-day. This maximum acceptable intake rate still exceeds the minimum RfD of 5×10^{-4} mg/kg-day corresponding to an HRS score of 1,000, and hence our HRS assignment of 1,000 would remain unchanged.

5.2 Use of the IEUBK Model to Calculate the Acceptable Daily Lead Intake Rate is Conservative

Section 5.1 derived an HRS toxicity factor value by using the EPA's IEUBK Model to determine the maximum daily lead intake rate that is consistent with a child having no more than a 5% chance of having a blood lead level exceeding 10 µg/dL. In this section, we show that the IEUBK Model is conservative in the sense that it often overstates blood lead levels corresponding to a specified level of lead exposure. If the IEUBK Model were more "neutral" in its predictions (*i.e.*, it tended to not overpredict blood lead levels), the estimated acceptable maximum daily lead intake calculated in Section 5.1 would have been even greater. In some contexts, use of a more neutral blood lead prediction model might yield an even lower HRS toxicity factor value for lead.

The most common context in which there are available both IEUBK predicted blood lead levels and empirically measured blood lead levels are Superfund sites in which the Agency has determined lead is a primary contaminant of concern. Table 5.2-1 compares summary statistics describing empirically measured blood lead levels and predicted blood lead levels at several sites where the model has been used. This table also appears in Appendix B of this document, where there is a more complete discussion of these comparisons.

Table 5.2-1
A Comparison of Empirical and Predicted Population Blood Lead Level Statistics

	Geometric Mean PbB (µg/dL)		Proportion of children with PbB > 10 µg/dL		95th percentile blood lead level (µg/dL)	
Community	Empirical	Predicted	Empirical	Predicted	Empirical [(a)]	Predicted [(b)]
Aspen, CO	2.6	4.9	0%	0.9%	6.0	8.0
Leadville, CO	4.8	9.5	8.2%	41%	11.4	22.0
Butte, MT	3.7	4.9			9.8	
	3.5	6.3	5.1%	16.8%	9.3	13.9
	3.7	4.9 to 5.9			9.8	
	3.7	9.1			9.8	
Bingham Creek, UT	2.45	2.93	0.7%	2.0%	4.8	7.0
Palmerton, PA	45	8.1	72%	20.4%	10.5	16.7
Granite City, IL	5.6	6.1	152%	19.0%	12.9	14.0

Two points should be kept in mind with respect to Table 5.2-1. **First,** the **"IEUBK"** Model predictions represent blood lead levels predicted by several versions *of* the model. **As** explained further in Appendix B, however, the most recent version (0.99d), which we used to calculate a maximum acceptable daily lead intake rate in Section **5.1,** is more "conservative" than the earlier models. This most recent version is therefore likely to overstate blood **lead** levels to an even greater degree than did the earlier versions of the model. Second, the data in Table **5.2-1** for the first **four** communities **(Aspen,** Leadville, Butte, and Bingham Creek) represent populations living in communities in which the primary source of lead contamination has **been** mining activities. The influence of this **type** of lead contamination **on** blood lead levels differs from the influence of lead contamination more typical of other types of communities (*e.g.*, smelters and urban environments). Nonetheless, data from Palmerton, PA and from Granite City, IL confirm that the **IEUBK** model is conservative in other settings **as** well.

One possible reason for the IEUBK Model's tendency to overestimate blood lead levels' may be its default assumptions regarding the bioavailability of lead. Investigators have conducted several studies of the bioavailability of lead in soil. While some studies indicate that as much as approximately 30% of lead in soil and dust may absorbed into the blood stream, other studies indicate this fraction is less than 30%. In other words, 30% is an upper end value, rather than a central tendency value. The following two studies provide examples of bioavailability values less than 30%

- Freeman *et al.* (1992): In this study, investigators fed Sprague-Dawley rats either mining waste soils containing 810 or 3908 µg/g lead, or lead acetate, for 30 consecutive days. The investigators assessed lead absorption by comparing the tissue lead concentration curves for rats administered lead acetate to the corresponding curves for rats administered lead in soil. Assuming that lead acetate is 100% soluble and that 50% soluble lead is absorbed into the blood stream, the results indicated that the absolute bioavailability of lead in mining waste soil may be 10% (based on blood lead data), 4.5% (based on bone lead data), or 4% (based on liver data).

- Schoof *et al.* (1995): Investigators administered to rats lead from a former smelter site or lead acetate at 4 different concentrations for 31 consecutive days. The authors concluded that the absolute bioavailability of lead in smelter soil is 20% (assuming that 100% of the lead acetate is soluble and that 50% of soluble lead is absorbed).

5.3 The Calculation of an Alternative HRS Score for Lead is Valid

The validity of the alternative HRS score that we have calculated depends on the validity of our assumption that our calculated maximum acceptable intake rate is comparable to the IUD values that serve as the basis for calculating HRS scores for other non-carcinogens. We believe that these values are qualitatively comparable.

We note that an IUD is defined to be "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population *(including sensitive subgroups)* that *is likely to be without an appreciable risk* of *deleterious effects* during a lifetime" (U.S. EPA, 1987, as quoted by

[7] There are other possible reasons why the IEUBK Model overstates blood lead levels. For example, default soil and dust ingestion rates may be too high. However, for the purpose of this analysis, we are interested only in assumptions built into the biokinctic portion of the model that may incorrectly inflate predicted blood lead levels. As explained in Appendix A, our estimate of the maximum acceptable daily intake of lead docs not depend on intake assumptions (like the soil and dust ingestion rate). Instead, it is a function of a target blood lead level (which reflects risk management considerations), the presumed fraction of lead that is absorbed, and the biokinetic slope factor embodied by the model.

U.S. EPA, 1997. Attachment 2, p. 4, emphasis added). We have italicized important qualifying words and phrases that have been included in this definition, and now describe why our maximum acceptable intake rate for lead is consistent with these terms.

Sensitive subgroups: Children are considered to be a sensitive subpopulation with respect to lead for several reasons. First, children absorb lead more readily than older individuals (U.S. EPA, 1986). Second, because their brains and nervous systems are still developing, it is thought that lead's potential neurotoxicity has a more significant influence on the cognitive function of children than it has on the cognitive function of adults (U.S. EPA, 1986; U.S. CDC, 1991; U.S. EPA, 1994b). The 10 µg/dL threshold used in our derivation of a maximum acceptable intake rate reflects conclusions based on the study of a substantial number of childhood populations. Hence, our maximum acceptable intake rate is appropriate for the childhood population.

More recently, U.S. EPA (1996c) has described pregnant women and women of childbearing age as a sensitive subpopulation because their exposure to lead may adversely affect their unborn child. However, the blood lead level of concern for these women is no lower than 10 µg/dL, and may even be slightly higher because fetal blood lead levels are believed to be somewhat lower than maternal blood lead levels.

Likely to be without appreciable risk U.S. CDC (1991) notes that adverse effects may occur at levels lower than the 10 µg/dL level specified by CDC as a threshold of concern. However, U.S. CDC states that "Some studies have suggested harmful effects at even lower levels [than 10 µg/dL blood lead], but the body of information accumulated so far is not adequate for effects below about 10 µg/dL to be evaluated definitively." In other words, there is inadequate evidence to conclude that adverse effects below 10 µg/dL are likely.

Two additional points should be noted here. First, even in the case of other non-carcinogens, the RfD is not a rigorous threshold below which we know there are no adverse effects. Often, the RfD is estimated using the No Observed Adverse Effect Level (NOAEL) reported in an animal bioassay. This dose corresponds to the treatment group receiving the lowest dose whose reaction did not differ

statistically from the control group. However, it is quite plausible that an adverse effect may occur below the **NOAEL** and would be detected if the study sample ***size*** were **larger.**

Second, although **U.S.** CDC **suggests** that **lead's** adverse effects may extend below 10 µg/dL, **CDC's** interpretation of the epidemiological evidence may be somewhat of an overstatement. Specifically, the adverse effects purportedly associated with exposure to lead **at** 10 µg/dL may be artifactual. ***As*** detailed in Appendix C to this report, the epidemiological literature on the neurological effects of lead in children has yielded inconsistent results at and above the 10 µg/dL level. Many of these studies may additionally be criticized for inadequately controlling confounders or incorrectly treating the simultaneous assessment of multiple comparisons. There is also some evidence suggesting lead's impact on cognitive ability may be reversible.

Deleterious effects: A number of investigators claim that the existence of **an** adverse effect associated with lead exposures below 10 µg/dL is supported by the observation of biological effects at lower blood lead levels. However, these effects, such **as** certain biochemical changes, do not constitute adverse effects since they **are** not clinically evident and do **are** not **known** to adversely affect any functional characteristics (*e.g.*, cognitive ability).

5.4 A Critique of U.S. EPA's Rationale for Assigning Lead the Highest HRS Toxicity Factor Value

Recall from Section 2.1 of this report that **U.S.** EPA advanced **three** reasons in support of the Agency's assignment of the highest possible HRS toxicity factor value to lead. **We** argue here that EPA has not applied these reasons in the context of other non-carcinogens. Hence, their application in the context of lead holds lead to a more stringent standard than other non-carcinogens, yielding **an** HRS toxicity factor value for lead that is inconsistent with its toxicity relative to other non-carcinogens.

First, EPA argues that, in the case of lead, there is ***"the absence of a demonstrated threshold for systemic toxicity"*** **(U.S.** EPA, 1990b, p. 2). However, evidence of an effect threshold in the *case* of other substances is often no more compelling than it is for lead, and often, it is **less** convincing. ***As*** noted in Section 5.3, evidence of lead's influence **below** 10 µg/dL is ambiguous at best. Moreover, RfDs for

many other substances are not known adverse effect thresholds. Instead, IUD values reflect animal bioassay results, the implications of which for humans are typically highly uncertain (*e.g.*, due to extrapolation of results across species, extrapolation of results from typical to sensitive members of the population, limitations introduced by experimental design, analytical technique limitations, and statistical limitations). Because of the uncertainty associated with the calculation of RfDs for many other substances, it is often impossible to determine the true value of an adverse effect threshold, or whether an effect threshold exceeding zero even exists. In short, there is a lack of strong evidence that there are adverse effects associated with blood lead levels at or below 10 µg/dL, and there is often a lack of evidence that there are no adverse effects below EPA's RfD values for other substances.

Second, EPA notes *"the cumulative sequestration of lead in the bone matrix and its subsequent release during pregnancy or osteoporosis"* (U.S. EPA, 1990b, p. 2). This phenomenon may occur, but it is not relevant to the determination of an HRS toxicity factor value. The criteria for determination of those values are clearly specified and are summarized in Section 2 of this report. The HRS toxicity factor value depends only on a substance's IUD or its cancer slope factor and weight-of-evidence category. That is, only a substance's impact on health is relevant in the determination of its HRS toxicity factor value. EPA does not consider sequestration, or body residence time in the case of other substances. For example, the fact that many other substances, such as PCBs, are sequestered in the body's lipotissue indefinitely is not relevant to the determination of their HRS toxicity factor values. Moreover, consideration of body residence time would lead to irrational score assignments. For example, like lead, fluoride is also incorporated into bone tissue (tooth enamel), and thus presumably remains in the body indefinitely. Fluoride can also be toxic at sufficiently high doses. Nonetheless, it would not make sense to assign to fluoride the highest possible HRS toxicity factor value solely because it can cause adverse health effects and because it remains in the body indefinitely. As with other substances, EPA should consider only the maximum acceptable daily intake for lead, and not whether lead remains in the body for an extended period.

EPA's third point is that *"the absence of an RfD and a cancer factor would give lead a toxicity value of 0 under the revised HRS which is inconsistent with the known health effects"* (U.S. EPA, 1990, p. 2). However, the fact that assigning a toxicity factor value of 0 to lead might lead to results EPA opposes does not justify assigning the highest possible HRS toxicity factor value to this substance.

In summary, EPA's reasoning is an inadequate basis for the selection of a human toxicity factor value. It does not reflect accepted scientific knowledge about the toxicity of lead and provides no quantitative consideration of lead toxicity or risks. Assigning lead the arbitrary toxicity factor value of 10,000 ignores EPA's standard approach to lead risk assessment that we used to calculate an alternative HRS toxicity factor value (see Section 5.1 and Appendix A in this report).

6 Conclusion

This report demonstrates that the original HRS toxicity factor value for lead of 10,000 and especially the revised HRS toxicity factor value for lead of 100,000 developed as part of the EPA's Sector Facility Indexing Plan, are inconsistent with the Agency's assessment of lead toxicity in other contexts. Use of HRS scores for lead specified as part of EPA's 1990 rule defining the HRS inappropriately ranks potentially hazardous waste sites, leading to the inclusion on the NPL of less hazardous sites that exhibit lead contamination in the place of sites that pose a greater threat to human health due to contamination by other substances. In the context of EPA's SFIP, the revised HRS scores will inappropriately highlight facilities releasing lead into the environment as posing a far more substantial threat to humans than other facilities that pose a far greater risk when judged by risk-based criteria developed by EPA in other contexts. We have developed an alternative HRS toxicity factor value that is 10 times lower than the value published by the Agency in 1990, and 100 times lower than the value developed by the Agency as part of the SFIP. This alternative value is far more consistent with EPA's risk assessment criteria and the available science on the toxicity of lead.

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Appendix A Derivation of an Alternative HRS Toxicity Factor Value for Lead

This appendix details the calculation of our alternative HRS factor value for lead of 1,000. This value reflects a calculated maximum acceptable daily intake for lead of 2×10^{-3} mgkg-day.

A.1 Identify the Median (Geometric Mean) Blood Lead Level Corresponding to a 5% Chance of Having a Blood Lead Level Exceeding 10 µg/dL.

Lead exposures that do not elevate the risk of having a blood lead level exceeding 10 µg/dL above 5% are deemed acceptable by U.S. EPA (U.S. EPA, 1994a; U.S. EPA, 1994b). Since the Agency assumes blood lead levels follow a lognormal distribution (U.S. EPA, 1994b), we must determine the blood lead level, PbB, such that $PbB \times GSD^{z} = 10$ µg/dL, where the GSD is assumed to equal 1.7 (a value consistent with Agency guidance as spelled out in U.S. EPA, 1994a), and z, which is the number of standard deviations to the right of the mean of a standard normal distribution corresponding to a cumulative probability of 95%, is equal to 1.645. In this case, the blood lead level is calculated as

$$PbB = \frac{10}{1.7^{1.645}} = 4.178\ \mu g / dL$$

A.2 Determine the Daily Lead Intake (µg/day) that will Produce a Blood Lead Level of 4.178 µg/dL

Since PbB is the product of the biokinetic slope factor (BSF), the fraction of ingested lead absorbed (A), and the quantity of lead ingested (Intake), the intake rate consistent with a blood lead level of 4.178 satisfies the relationship

$$Intake = \frac{PbB}{BSF \times A} = \frac{4.178}{BSF \times A}$$

The biokmetic slope factor *can* be calculated by regressing IEUBK predicted blood lead levels against lead uptake values. Here, we have modeled lead uptake and blood lead levels for 2-3 year-old children, using default values for all IEUBK parameters except soil lead concentration, which we have varied from 150 µg/g to 200 µg/g. The slope of the regression line (which is equal to the BSF) is 0.3681.

Finally, we assume that the fraction of ingested lead that is absorbed is 40%, as discussed in the main text of this report.

The Intake value consistent with a blood lead level of 4.178 µg/dL is 4.178 ÷ (0.3681 x 0.40), or 28.37 µg/day.

A.3 Intake Rate Expressed in mg/kg-day

Here, we simply divide the result just calculated in Section A.2 by the average body weight for a 2-3 year-old child. Table 7-2 in the U.S. EPA's 1996 Exposure Factors Handbook (U.S. EPA, 1996) lists the average body weight of 2 year-olds as 13.3 kg, and the average body weight of 3-year-ob as 15.3 kg. Hence, the average body weight for a 2-3 year-old child is approximately 14.3 kg. The intake rate yielding a 5% risk of having a blood lead level above 10 µg/dL is therefore 28.37 µg/day ÷ 14.3 kg, or 1.98 µg/kg-day. This value is approximately equal to 2×10^{-3} mg/kg-day.

A.4 The Alternative FIRS Toxicity Value for Lead

As detailed in Table 2-24 non-carcinogens with RfD values between 5×10^{-4} and 5×10^{-3} mgkg-day are assigned an HRS toxicity value of 1,000. Our calculation indicates that the maximum acceptable intake rate for lead falls in this range.

A.5 References

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Appendix B EPA'S Use of the IEUBK Model Consistently Overstates Blood Lead Levels

This appendix presents information demonstrating that the EPA's Integrated Exposure Biokinetic Model is conservative in the sense that it tends to overstate actual blood lead levels associated with a specified level of lead exposure. Here, we compare blood lead levels measured at several mining and smelting sites to blood lead levels predicted using EPA's IEUBK model, arguing that as it has been used by EPA, the model consistentlyyields predictionsthat overstate actual lead exposure. Specifically, EPA's use of the model tends to overstate both the central tendency of the population distribution (*e.g.*, the geometric mean), the proportion of children with elevated blood lead levels (*e.g.*, in excess of CDC's concern threshold of 10 µg/dL), and the upper percentile values of the blood lead level distribution (*e.g.*, the 95th percentile of the distribution).

The development of multiple versions of the IEUBK model complicates these comparisons since the models tend to predict different blood lead levels. For the purpose of this discussion, the most recent version of the software (version 0.99d) is of primary interest. It turns out that earlier versions of the model tend to predict lower blood lead levels than version 0.99d (Bowers, 1994). Hence, a comparison demonstrating that earlier versions of the software overpredicted actual blood lead levels demonstrates that version 0.99d would have overpredicted these values as well (but to an even greater extent). It should also be noted that blood lead levels in the general population have been declining over time due to the phase out of leaded gasoline and the declining level of lead in the nation's food supply. Because these factors inflated blood lead levels in the past, comparisons of predicted and measured blood lead levels for the purpose of evaluating the IEUBK software must be restricted to only the most recent data sets.

The following table lists several sets of comparisons between blood lead levels predicted by the IEUBK model and empirically measured blood lead levels for Aspen, Colorado, Butte, Montana, Leadville, Colorado, Palmerton, Pennsylvania, and Granite City, Illinois. The discussion that follows discusses each of these comparisons in greater detail.

Table B-1
A Comparison o Empirical and Predicted Population Blood Lead Level Statistics

	Geometric Mean PbB (µg/dL)		Proportion of children with PbB > 10 µg/dL		95th percentile blood lead level (µg/dL)	
Community	Empirical	Praiicted	Empirical	Predicted	Empirical (a)	Predicted (b)
Aspen, CO	2.6	4.9	0%	0.9%	6.0	8.0
Leadville, CO	4.8	9.5	8.2%	41%	11.4	22.0
Butte, MT	3.7	4.9			9.8	
	3.5	6 3	5.1%	16.8%	9 3	13.9
	3.7	4.9 to 5.9			9.8	
	3.7	9.1			9.8	

Notes:

(a) *Empirical 95th percentile values were estimated for Aspen, Leadville, and Butte using the assumption that the blood lead distribution is log normal. The assumed GSD values are: Aspen, 1.66: Leadville, 1.69 (calculated from the observed GM = 4.8 µg/dL and the observed proportion of children with blood lead levels above 10 µg/dL (8.2%)); Butte, 1.81: and Granite City, 1.66. For Bingham Creek and Palmerton, the 95th percentile value was available directly.*

(b) *IEUBK predicted 95th percentile values were estimated for Aspen and Bune using the assumption that blood lead levels are lognormally distributed. The GSD was calculated using the predicted geometric mean and the predicted proportion of children with PbB > 10 µg/dL.*

Aspen, Colorado

Blood lead levels were measured among 28 children aged 6 to 71 months living in Aspen, Colorado by the Colorado Department of Health (1992). The geometric mean blood lead level in this group was 2.6 µg/dL and no blood lead level exceeded 10 µg/dL. The Smuggler Mountain Technical Advisory Committee (1993) used the IEUBK model to predict blood lead levels. Using site-specific soil lead concentrations, and default values for other model parameters, the Committee estimated a geometric mean blood lead level of 4.9 µg/dL. Assuming an inter-individual geometric standard deviation of 1.66, they also

predictedthat 0.9% of the population would have blood lead levels above 10 µg/dL. However, because this fraction is so small, it is not possible to know whether it truly differs from the observed proportion of zero percent above 10 µg/dL. Corresponding empirical and IEUBK-predicted 95th percentile values for the blood lead distribution are 6.0 µg/dL and 8.0 µg/dL, respectively.

Leadville, Colorado

Blood lead levels measured in Leadville, Colorado during 1991 among 316 children (Bornschein, 1994) had a geometric mean of 4.8 µg/dL, with 8.2% exceeding 10 µg/dL. Weston (1991), working for EPA, used version 0.5 of the IEUBK software with site-specific dust and .soil lead concentrations and default values for all other parametersto predict blood lead levels for this population. The results predicted a geometric mean blood lead level of 9.5 µg/dL, and that 41% of the children in the population would have blood lead levels above 10 µg/dL, far more than the observed 8.2%. Correspondingempirical and IEUBK-predicted 95th percentile blood lead levels were 1 1.4 µg/dL and 22.0 µg/dL, respectively.

Butte. Montana

Several investigatorshavecompared predictedand measured blood lead levels for children living in Butte, Montana. Using version 0.6 of the IEUBK software, Griffin *et al.* (1993) predicted blood lead levels for this populationto values measured by Bomschein. Empirical blood lead levels had a geometric mean of 3.7, whereas the predicted blood lead levels had a geometric mean of 4.9. In a presentation to EPA, ARCO (1991) noted that observed blood lead levels had a geometric mean of 3.5 µg/dL with 5.1% of the measurements above 10 µg/dL, whereas blood lead levels predicted by the IEUBK model had a geometric mean of 6.3 µg/dL with 16.8% exceeding 10 µg/dL. EPA (1993) used version 0.61 of the IEUBK software to predict blood lead levels for 196 children using some site-specific parameter values, as well as default settings for other quantities. Using a "high-end" value for the soil and dust ingestion rate, the EPA predicted a geometric mean blood lead level of 5.9 µg/dL, while using a "midpoint" value for this parameter yielded a geometric mean blood lead level of 4.9 µg/dL. The observed geometric mean blood lead level of 3.7 µg/dL was lower than both these estimates. Finally, an EPA workgroup reviewing the IEUBK model (EPA, 1992)showed that the IEUBK model predicts a geometric mean blood lead level of 9.1 µg/dL when default values are used for all parameters, far higherthan the aforementionedobservedgeometric blood lead

level of 3.7 µg/dL. The 95th percentile blood lead level correspondingto the empirically observed blood lead level statisticsranged from 9.3 to 9.8 µg/dL. Only the results from the EPA workgroup (EPA, 1992) could be used to estimate an IEUBK-predicted 95th percentile blood lead level. The 13.9 µg/dL result is much higherthan the inferred empirical value of 9.3 to 9.8 µg/dL.

Bingham Creek

The IEUBK model also overpredicts blood lead levels at Bingham Creek. Empirical blood lead levels were compared to levels predicted by version 0.99d for the 283 "high-risk"children surveyed by the University of Cincinnati. When available, dwelling-specific soil, dust, and drinking water lead concentrationswere used for each child. Default values were used for other parameters. On average, the IEUBK model overpredicted blood lead levels by 20%. The predicted geometric mean blood lead level was 2.93 µg/dL, nearly 20% greater than the actual geometric mean of 2.45 µg/dL. Empirically, only 0.7% of the children had blood lead levels above 10 µg/dL, compared to the IEUBK-predicted proportion of 2.0%. However, because these fractions are so small, the importance of this difference is difficult to determine. Finally, the empirical 95th percentile blood lead level (4.8 µg/dL) is substantially less than the IEUBK-predicted 95th percentile blood lead level of 7.0 µg/dL.

Palmerton Pennsylvania

Researchers at the University of Cincinnati measured blood levels in children less than 72 months old (n=108) living in Palmerton, PA (University of Cincinnati, 1996). The geometric mean in this group was 4.5 µg/dL with 7.2% of the children having blood lead levels over 10 µg/dL. Gradient Corporation used version 0.99d of the IEUBK model with default values to predict a blood lead geometric mean of the University of Cincinnati dataset to be 8.1 µg/dL with 20.4% of the levels over 10 µg/dL. This prediction was a gross over-estimation of what was empirically determined. Additionally, 95th percentile blood levels were 16.7 µg/dL and 10.5 µg/dL for the IEUBK-predicted and empirical values, respectively.

Granite City, Illinois

A study directed by the Agency for Toxic Substances and Disease Registry (ATSDR) and carried out by the Illinois Department of Public Health (IDPH) recorded blood lead levels for 490 children living in Granite City Illinois (U.S. EPA, 1994). Blood lead levels among the surveyed population had a geometric mean value of 5.6 µg/dL. Use of the IEUBK Model (version 0.99d) to predict blood lead levels using default parameters yielded a geometric mean of 6.1 µg/dL. Finally, empirical data indicated that 16% of children in Granite City had blood lead levels exceeding 10 µg/dL, while the corresponding IEUBK-predicted value is 24%. There is no information available regarding the value of the 95th percentile blood lead level.

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Appendix C The 10 µg/dL Target Blood Lead Level Ensures EPA's Assessment is Conservative

Although U.S. EPA typically interprets the 10 µg/dL as a maximum acceptable blood lead level, scientific research of the health effects associated with lead exposure indicate that this blood lead level has a substantial probability of being below the level of exposure at which any health effects of consequence might occur. Our calculation of an alternative HRS toxicity value, which is based on the 10 µg/dL threshold, is therefore conservative since it is likely that, even if a child's blood lead level moderately exceeds the target of 10 µg/dL, that child will not experience any substantive health impairment.

That the 10 µg/dL blood lead level target is conservative can be inferred from several facts:

- The Centers for Disease Control (the governmental body that first developed this target) does not recommend environmental intervention until blood lead levels exceed 14 µg/dL. Only if a large proportion of children in a community have blood lead levels between 10 and 14 µg/dL does the CDC recommend prevention activities. For children with blood lead levels between 15 and 19 µg/dL, CDC recommends "nutritional and educational interventions and more frequent screening" (U.S. CDC, 1991, p. 3). Environmental intervention is recommended only if blood lead levels in this range persist over time.
- The extensive body of epidemiological research into the association between lead exposure in children and impaired cognitive function has yielded inconsistent results near and well above the 10 µg/dL level.
- The epidemiological studies investigating the association between blood lead levels and cognitive development are often plagued by problems that might lead them to overstate the influence of lead exposure. These problems include: inadequate control of confounders, and simultaneous assessment of multiple associations.
- The influence of lead on cognitive ability may be reversible.

We discuss each of these issues in turn.

C.1 CDC Does not Recommend Environmental Intervention at 10 µg/dL

The U.S. Centers for Disease Control first proposed the 10 µg/dL blood lead level of concern in its 1991 statement, entitled, "Preventing Lead Poisoning in Young Children" (U.S. CDC, 1991). Although the document states that "the 1985 intervention level of 25 µg/dL is... being revised downwards to 10 µg/dL" (p. 1), CDC notes that "10 µg/dL is the lower level of the range at which effects are now identified..." (p. 2). As a result, CDC adopted a multi-tier approach, as detailed in Table C-1.

Table C-1
Government Criteria for Childhood Lead Exposure: CDC's Multi-Tiered Approach

Blood Lead (µg/dL)	CDC Recommended Action
Below 10	No action
10-14	Rescreen. If many children are at or above 10 µg/dL, implement community level interventions.
15-19	Rescreen. Consider environmental investigation and abatement if levels persist.
20 and above	Medical evaluation. Environmental assessment and remediation.

Note that CDC does not recommend immediate intervention to address an individual child until blood lead levels reach 20 µg/dL. In fact, CDC does not refer to 10 µg/dL as "lead poisoning" and even states that "Blood lead levels between-10 and 14 µg/dL are in a border zone" (p. 2).

C.2 Epidemiological Data are Inconsistent on the Association Between Childhood Lead Exposure and Compromised Cognitive Function

Studies investigating the association between increased blood lead levels and compromised cognitive function can be divided into two categories: 1) Cross-sectional studies, which compare performance on cognitive ability tests (like the IQ test) at a single point in time to blood lead levels measured at a single point in time; and 2) Longitudinal studies, which track both cognitive performance and blood lead levels over an extended period of time (typically, in the case of lead studies, from birth through at least early childhood).

Before summarizing the quantitative findings of these studies, it is important to note three observations. **First,** the effects reported by these studies *are* "subclinical," meaning that they *are* too subtle *to* observe in a single child. They can only be quantified by statistically comparing cognitive ability among a large number of children.

Second, the effects reported by these studies *are* often the largest effect that researchers could identify. Often, the studies yield many *sets* of blood lead-cognitive ability results. For example, because a longitudinal study measures both blood lead levels and cognitive ability at many points in time, there *are* many sets of blood lead-test score comparisons (*e.g.*, the association between blood lead levels at age 6 months and test scores at age 3, or the association between blood lead levels at age 18 months and test scores at age 3). In many cases, it is the strongest of these associations that is purported to represent the "true" influence of lead on cognitive ability. We comment on this issue further in Section C.3.

Third, many of the studies are based on populations with blood lead levels substantially exceeding 10 µg/dL. If the incremental influence of lead decreases, or even vanishes, below some blood lead level, than the results of these studies would be irrelevant even if there were no other problems.

The longitudinal studies *are,* for the most part, the newest and most sophisticated of the epidemiological studies of the association between blood lead and cognitive ability. Longitudinal studies conducted in five cities serve as partial support for CDC's identification of 10 µg/dL as a threshold of concern. The cities in which these studies were conducted *are:* Boston, MA, Cincinnati, OH, Cleveland, OH, Port Pine, Australia, and Sydney, Australia. The reported influence of blood lead levels recorded at age 2 on subsequent cognitive test scores (often IQ tests) often exceeds the reported influence of average post-natal blood lead levels, blood lead levels measured just after birth (see Figure 1 in Pocock, 1994).

Table C-2 summarizes the results from these five longitudinal studies for the association between blood lead levels recorded at approximately age 2 years and IQ test scores recorded later during childhood. This summary is based on a review of the literature conducted by Pocock *et al.* (1994). The review omits discussion of two additional longitudinal studies – the Yugoslavia study (Graziano, 1990) and the Mexico City study (Rothenberg, 1989) – presumably since, at that time, these studies had not yet reported results. Two other studies may be considered longitudinal in nature – the Nordenham study

(Winneke et al., 1989), and the Glasgow study (Moore et al. 1989), but study design and measurement methodology differences make comparisons with the studies listed in Table C-2 difficult (Volpe et al., 1992).

Table C-2
Longitudinal Study Results

Change in Test Score Associated with an Increase in Blood Lead Levels from 10 to 20 µg/dL						
Study Location	Source	Blood Lend Level Measurement Used	Age at which IQ Scores Assessed	Effect Magnitude'	Statistically Significant?	Population Mean Blood Lend Level[b]
Port Pirie	Baghurst et al. (1992)	Avg: 0 to 3 Years	7	-3.3	YCS	21.2
Cincinnati	Dietrich et al. (1993)	3 Years	6.5	-1.3	No	17.5
Cleveland	Ernhart et al. (1989)	2 Years	5	-1.1	No	16.7
Sydney	Cooney et al. (1991)	1-2 Years	7	0.39	No	14.2'
Boston	Bellinger et al. (1992)	2 Years	10	-5.8	Yes	6.8

Source: Adapted from Pocock et al. (1994), Table I.

Notes:

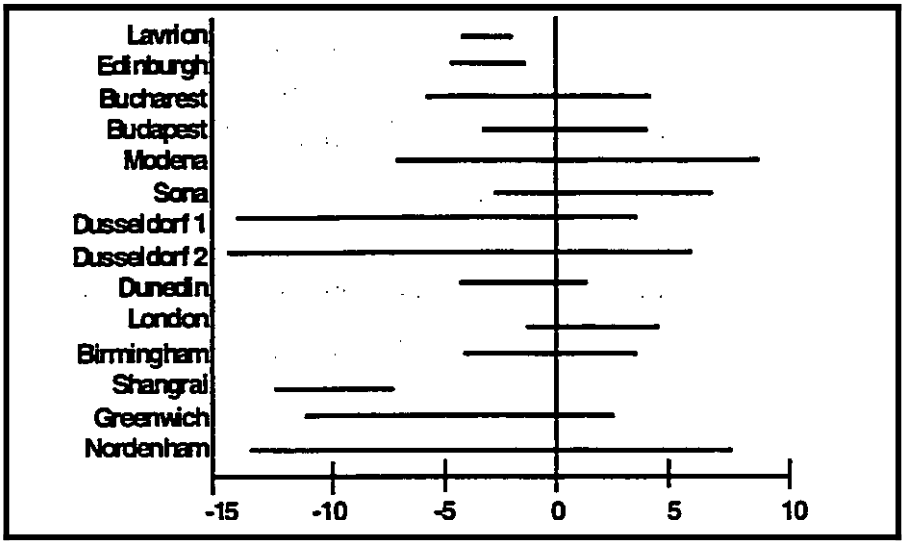
a *The "Effect Magnitude" represents the predicted change in test scores associated with a doubling of blood lead levels from either 5 µg/dL to 10 µg/dL, or from 10 µg/dL to 20 µg/dL. Tests include the IQ (typically for children ages 3 years and higher) and various developmental tests for younger children. These developmental tests are often scaled so that point score differences are comparable to point score differences for the IQ.*

b. *Represents geometric mean blood lead level assessed at age detailed in column 3 of table. The arithmetic mean blood lead level, which is not reported, most likely exceeds the geometric mean value.*

Note that of the 5 studies, only 2 yielded results that are statistically significant. The size of the effects reported also differ substantially, a finding not expected when measuring a *true* phenomenon. The Sydney study reports a slightly positive association between blood lead levels and cognitive function, while Boston reports that a doubling of blood lead levels decreases cognitive test scores by nearly 6 points. It should also be noted that blood lead levels among participants in these studies were often substantially higher than levels now typical in the U.S. population (geometric mean value of approximately 3 µg/dL – Brody et al., 1994), or even CDC's 10 µg/dL concern threshold. To the extent that lead's incremental effect is greater at higher levels, these results may overstate the influence of lead at levels more relevant to the United States.

The cross-sectional studies of the association between blood lead levels and cognitive function also yield a wide range of results, as illustrated in Figure C-1.

Figure C-1
Cross-sectional Study Results: The Association Between Blood Lead Levels (An Increase from 10 μg/dL to 20 μg/dL) on IQ Test Scores[a]



Adapted from Pocock et al., 1994, Table 2.

Notes:

a *Lines denote the span of the 95% confidence interval for the reported effect.*

The central estimate of these study results span a wide range of values. Moreover, many of the confidence intervals (11 out of 14) include zero).

C.3 Characteristics of Epidemiological Studies that Tend to Inflate the Estimated Association Between Blood Lead Levels and Cognitive Ability

Assessing the association between blood lead levels and cognitive ability is difficult, and some reviewers of the literature have concluded that many studies have characteristics that lead them to overstate the magnitude of this potential association. This section reviews these pitfalls.

C.3.1 Inadequate Control of Confounders

Inadequate control of confounders is potentially the most serious problem leading to potential overestimation of the potential association between blood lead levels and cognitive function. A "confounder" is a quantity that is associated both with the purported explanatory variable (in this case, blood lead) and the outcome of interest (in this case, cognitive function). If the confounder truly influences the outcome of interest and the study does not adequately control for that influence, then the study will find a "spurious" association between the perported explanatory variable and the outcome of interest. Dr. Allan Kaufman, an expert in the field of child psychology who has developed cognitive ability tests used in several studies of the influence of increased blood lead levels in children, has outlined several potentially important confounders that he believes have been inadequately addressed in the majority of blood lead level studies (Kaufman, 1996).

Dr. Kaufman starts by stating that the correlation between two variables (*e.g.*, blood lead levels and cognitive function) does not necessarily indicate the presence of causation. For example, he notes that Hopkins and Glass (*Basic Statistics for the Behavioral Sciences,* 1978, pp. 144-145) warn that:

> The presence of a correlation between two variables does not necessarily mean there exists a causal link between them. Even though concomitance (correlation) between events can be useful in identifying causal relationships when coupled with other methodological approaches, it is a dangerous and potentially misleading test for causation when used alone... [T]he relationships that exist among variables in behavioral and social sciences are almost always too complex to be explained in terms of a single cause..... Failure to recognize that correlation may not mean causation is a widespread logical error.

Kaufman acknowledges that studies of the association between blood lead levels and cognitive function have improved over time with regard to the control of potential confounders. However, he states that, "there is still a long way to go in this area" (p. 5). Specifically,

> The variables that are undoubtedly most related to a young child's ingestion of lead are the hardest to assess accurately. Such variables involve parenting skills, parenting styles of childrearing, parental time spent with the child, the skills and styles of key caretakers other than the parents, and so forth. These ***variables have not been measured accurately in any of the 26 studies*** [Kaufman reviewed as among the best of the available analyses] (emphasis added, p. 5).

These variables most likely influence child performance on tests of cognitive ability, such as the IQ. Kaufman adds that other factors may act as confounders. and that these factors are often not adequately controlled. He concludes (pp. 8-9) that,

> ... most studies of lead and IQ even when limited to the 'best' available studies have failed to control for important parenting variables, subtle socioeconomic variables and medical variables, and they have been unable to control for confounds due to what are undoubtedly a plethora of unknown but potentially potent unknown variables. The net result is to make the results of the lead studies inconclusive and uninterpretable.

He states further that, "it is quite possible if not highly probable that much or all of the so-called IQ loss due to lead level is due to ... other confounding factors" (p. 9).

Kaufman offers additional evidence suggesting that reported associations between IQ and lead exposure may reflect inadequately controlled socioeconomic factors. He points out that in the majority of studies that have reported such an association, the portion of the IQ test that is most strongly associated with lead exposure is the "verbal" section, rather than the "performance" section. Such a fmding is inconsistent with the hypothesis that lead results in neurological damage since neurological damage is more strongly associated with performance IQ than it is with verbal IQ. Moreover, Kaufman points out that verbal IQ is more strongly associated with socioeconomic status than is performance IQ. Because lead exposure appears to affect verbal IQ, Kaufman concludes that such fmdings may reflect inadequately controlled socioeconomic confounders, rather than neurological damage. Kaufman quotes Smith's review of lead-IQ studies (*Journal of the American Academy of Child Psychiatry, 1995*, p. 31):

> In most, but not all studies.., differences between lead groups in IQ scores are predominantly in the verbal IQ, and less so in performance IQ.... This is inconsistent with clinical experience which shows that verbal IQ is more sensitive to socioeconomic factors, while performance IQ is more vulnerable to neurotoxic insult such as excessive alcohol intake.

C 3 3 Inadequate Measurement of Parental IQ

Kaufman singles out parental IQ as a confounder that has a potentially enormous impact on study results and notes that the vast majority of studies have either measured parental IQ poorly or not at all. He begins by stating that,

> Lead researchers have become aware that one of the strongest correlates both of IQ and lead level in a young child is the child's parental IQ, and that this potential confound must be controlled in lead-IQ studies. Parental IQ is related to SES [socioeconomic status] and to genetic factors; controlling for it as a confound, even when SES is otherwise controlled, is absolutely essential for a competent research design (p. 10).

Of the 26 studies included in Kaufman's review, 8 failed to measure parental IQ at all. Among the remaining 18 studies, only two (p. 10)

> administered the accepted criterion of adult intelligence, the Wechsler Adult Intelligence Scale-Revised or WAIS-R (Baghurst *et al.*, 1992; McMichael *et al.*, 1994 - both reporting on the Port Pirie study).

Kaufman finds that

> The net conclusion is that even though researchers have claimed to control for the key potentially confounding variable of parents' IQs, nearly all studies have done an unimpressive job of it.

C 3 3 Simultaneous Assessment of Multiple Comparisons

One of the major problems that statistical inference attempts to address is the acceptance of a spurious hypothesis that appears to be true based on a random sample of data, but which is not true for the population from which the sample was drawn. For example, if one were to choose two coins from a container containing thousands of coins, and get two heads when the two coins were flipped, it would be inappropriate to conclude that the container of coins are "loaded" so that a coin flip yields heads more often than it yields tails. The fact of the matter is that, when only two coin flips are involved, there's a 25% that the result will be two heads. There's also a 25% chance that there will be two tails. That

m that there's a 6 chance that the sample will be consistent with an) g bias in the population of coins from which they were drawn even if that ti of coins is fair.

To avoid such spurious inferences, statisticians have established criteria to ensure that a hypothesis that is being tested is not accepted unless the data supporting it could not arise by chance alone with less than a 5% probability. That means that it is possible, but improbable, that the tested hypothesis will be incorrectly accepted.

While the vast majority of studies testing the hypothesis that there is an association between blood lead levels and IQ purport to adhere to the 5% criterion, these studies violate this criterion by testing multiple associations at the same time. A simple example shows how simultaneous testing of a multiple hypotheses can yield a spurious finding that one of the hypotheses is likely to be true. Suppose we wished to test the hypothesis that coins drawn from a container always come up heads when flipped. We test this hypothesis by flipping five coins and accept our tested hypothesis only if all five come up heads. The chance that all five coins will come up heads if the coins are fair is $(\frac{1}{2})^5$, or approximately 3%. Now suppose that we test 20 sets of five coins each. It turns out that there is nearly a 50% chance that at least one of these sets of five coins will come up heads even if the coins are fair. Concluding the coins are biased based on the finding that one set of coins came up heads would be an invalid inference.

Unfortunately, this same logical fallacy has found its way into a number of the studies investigating the association between blood lead and cognitive function. The problem has its greatest potential among the longitudinal studies since there are so many measurements of both blood lead and cognitive function over time, and hence so many potential comparisons. Kaufman points out (p 13) that the Bellinger-Needleman longitudinal study of children in Boston (Bellinger et *al.*, 1992) made 21 simultaneous comparisons. Of these, 2 were "statistically significant." However, it is not unlikely that 2 of 21 tests of association would yield statistically significant results at the 5% level even if no association existed in reality[8].

[8] The probability of 2 or more associations yielding statistically significant results at the 5% level even if no associations exist in reality is approximately 28%.

C.4 Lead's Effect on Cognitive Ability May be Reversible

The extent to which moderately elevated body lead burdens are a serious problem depends on the degree to which lead's impact on cognitive function persists after relatively high levels of exposure more common in childhood end. At least one longitudinal study of the relationship between lead exposure in childhood and subsequent cognitive function indicates that lead's influence is at least in part reversible.

The Boston longitudinal study of lead exposure (Bellinger *er al.*, 1987; Bellinger *et al.*, 1990) followed a cohort of approximately 250 children from birth, recording antenatal blood lead levels (represented by umbilical cord blood lead levels) and postnatal blood lead levels during the first two years of life approximately every six months. Bellinger *er al.* measured cognitive ability using the Mental Development Index of the Bayley Scales of Infant Development (which, like the IQ test, has a mean of 100 points and a standard deviation of 16 points'). Bellinger *et al.* administered the Bayley Scales to study subjects at approximately ages 1, 6, 12, 18, and 24 months. During this period, the Bayley scores among children in the "high prenatal exposure group" (cord blood lead levels exceeding 10 μg/dL) were approximately 5 points lower than the Bayley scores among children in the "low prenatal exposure group" (cord blood lead levels less than or equal to 3 μg/dL).

The 1990 follow-up report on this cohort (Bellinger *et al.*, 1990) reports that "By age 5 years... [children with umbilical cord blood lead levels of 10 to 25 μg/dL] appear to have recovered from, or at least compensated for [early exposure to lead]" (p. 5). In addition, the recovery among the high prenatal exposure group was most pronounced among those children with the lowest blood lead levels at approximately 5 years of age. Other factors associated with improved recovery were: "higher socioeconomic status, higher Home Observation for Measurement of the Environment scores, higher maternal IQ, and female gender" (p. 5). Although these results from the Boston longitudinal study provide a single example of lead exposure whose effects may be reversible, the results lend credibility to the hypothesis that any potential adverse impact of moderately elevated blood lead levels on cognitive performance may not be permanent.

[9] The Mental Development Index of *the* Bayley *scales* assesses an infant's "sensory-perceptual acuities, discriminations, and the ability to respond to these; *the* early acquisition of 'object constancy.' memory, learning. and problem salving ability; vocalization and the beginnings of verbal communication; and early evidence of the ability to form generalizations and classifications, which is the basis for abstract thinking" Bayley N. Baylcy scales of infant development. N m York: The Psychological Corporation, 1969. As quoted in Bellinger, *et al.* 1987 (p. 1038).

Bellinger has commented further on the issue of the potential reversibility of lead's impact on cognitive function (Bellinger, 1997). Here. he states that animal models are necessary to ascertain the reversibility of lead's effects since such experiments eliminate problems introduced by confounders, and allow the careful manipulation of exposure levels over *time.* Bellinger cites animal studies (Rice, 1993) that purport to demonstrate behavioral deficits "at age 10 years in animals whose blood lead level peaked at 25 µg/dL at 300 days of age and whose steady-state levels remained below 15 µg/dL thereafter" (Bellinger, 1997, p. 282). However, the evidence against reversibility seems to be strongest in the case of behavioral measures (rather than cognitive ability). As Bellinger concludes, "Whether medical treatments or environmental interventions that reduce children's blood lead levels reverse or limit exposure-related decrements in cognitive performance remains uncertain" (p. 282).

C.5 Conclusion

The preceding discussion highlights sources of uncertainty underlying the assumption that increased blood lead levels in the vicinity of the CDC's threshold of concern (10 µg/dL) are associated with an adverse health effect in children manifest in terms of compromised cognitive function. Because there is doubt surrounding the existence of adverse health effects at this level, it must be concluded that the use of this threshold, *per se,* builds a conservative element into maximum acceptable intake levels developed using this blood lead level threshold. Even if all the assumptions that go into the calculation are not conservative, we can be confident that protection at the 10 µg/dL level constitutes a margin of *safety.*

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